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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/753,107

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Anton Bittner

ORT1563NP

2785

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7590

06/01/2006

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EXAMINER

ZHOU, SHUBO

ART UNIT

PAPER NUMBER

1631

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/753,107

Applicant(s)

BITTNER ET AL.

Examiner

Shubo (Joe) Zhou

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 13 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) 1-6 and 8-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 7 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>9/1/04</u> . | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Election/Amendments***

1. Applicants' election, with traverse, of Group III (claim 7) in the response filed 3/13/06 is acknowledged. The traversal is on the ground that while the inventions of groups I-V are distinct, examining all of them would not impose a serious search burden to the Office as evidenced by the examiner's common classification of the claims for the groups. No further specific argument is provided. This is not found persuasive because although the claims of the groups belong to a common class, as pointed out by applicants, the inventions of the groups are distinct as they comprise distinct steps, produce distinct results, and they are mutually exclusive and not obvious variants. As such, examining all the inventions would involve distinct search strategies and the search would not be coextensive. Therefore, examining all the groups would impose serious search burden to the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-36 are currently pending, claim 7 is under examination and claims 1-6 and 8-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 3/13/06.

### ***Priority***

2. It is noted that this application appears to claim subject matter disclosed in prior Application No. 60/438,002, filed 1/6/03. A reference to the prior application must be inserted

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as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due

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under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

### ***Information Disclosure Statement***

3. The Information Disclosure Statement filed 9/1/04 has been entered and references therein have been considered. Initialed copies of the form PTO-1449 are enclosed herein.

### ***Specification***

4. The specification is objected to because of the following:

Trademarks are used in this application, such as GENBANK on page 16 and DYNABEADS on page 23. Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

***Claim Rejections-35 USC § 101***

5. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claim 7 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claim is drawn to a process for quality control of microarray analysis of gene expression. The process comprises retrieving intensity data from replicate spots on a hybridized microarray, calculating a mean and a standard deviation for the data, generating a Z-score transformation for each spot, calculating a first percentage of spots for which the absolute value of the z-score exceeds 1, comparing the percentage with a predefined value, calculating a second percentage for which the absolute value of the z-score exceeds 2, comparing this percentage with a predefined value, calculating a third percentage for which the absolute value of the z-score exceeds 3, and comparing this third percentage with a predefined value.

Consideration of the "Computer-Related Inventions", section 2106 of the MPEP, part IV, and the "Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility" (OG Notices: 22 November 2005, available from the PTO website at <http://www.uspto.gov/web/offices/com/sol/og/2005/week47/og200547.htm>, a copy of which is enclosed herein) revealed that the instant claim is directed to non-statutory subject matter. The

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claimed invention is a process of manipulating and converting data that neither results in any physical transformation outside of the computation, nor produces a useful, concrete and tangible result. The method steps of the claim merely retrieve gene expression data, calculating means, deviations, z-scores and percentages, and comparing the percentages with predefined values. The end result of the method steps is a comparison between certain percentages and predefined values, which is not a useful, concrete and tangible result.

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (Genome Biology, 2002, 3(11): research0062.1-0062.12) in view of Churchill, G.A. (Nature Genetics Supplement, Vol. 32, December 2002, pages 490-495).

The claim is drawn to a process for quality control of microarray analysis of gene expression comprising retrieving intensity data from replicate spots, calculating a mean for the intensity data for the spots, calculating a standard deviation for the data, generating a Z-score transformation for each spot, calculating a first percentage of spots for which the absolute value of the z-score exceeds 1, comparing the percentage with a predefined value, calculating a second percentage for which the absolute value of the z-score exceeds 2, comparing this percentage with a predefined value, calculating a third percentage for which the absolute value of the z-score exceeds 3, and comparing this third percentage with a predefined value. Absent an explicit definition in the specification, the term “replicate spots” is interpreted as including duplicate spots on the same array.

Yang et al. disclose a method for assessing variability and increasing reproducibility of microarray analysis by using replicates. They devised a simple procedure for identifying and eliminating low-quality data for replicas within and between microarray slides. See page 0062.1, Abstract. The method comprises using self-self hybridization, i.e. aliquots of the same RNA being labeled separately with Cy3 or Cy5 dyes and co-hybridized to the same cDNA microarray that contains 19,200 elements (9,600 elements in duplicate). See page 0062.2, right column.



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Since all these spots comprise duplicates of each element, they are interpreted as being replica spots. Among other things, Yang et al. tested the self-self hybridization using RNA sample from a cell line KM12L4A. In the method, intensity data for each spot is obtained and normalized, and a standard z-score is calculated based on intensity. Specifically, using a sliding window of fixed width in  $\log_{10}(\text{Cy5} \times \text{Cy3})$ , the local mean and SD was calculate for each gene using the normalized data. Figure 3a on page 0062.5 depicts the results of such a calculation for cell line KM12L4A, with data less than 1SD shown blue, between 1SD and 2SD in green, and greater than 2SD in red, respectively. Note that the copy of the reference provided to applicants as enclosed herein is a black and white copy of the original color picture, which is available from Genome Biology online at <http://genomebiology.com/content/pdf/gb-2002-3-11-research0062.pdf>. For the convenience of the present discussion, based on the original Figure 3a, the portions of the figure represented by colors of blue, green and red are indicated with B, G and R, respectively, by the examiner in the copy enclosed herein.

It is pointed out that while Yang et al. do not explicitly state that the z-score is calculated by subtracting the mean from the intensity data of a replica spot and dividing by the standard deviation for the intensity data, as recited in claim 7, it would be readily apparent to one of ordinary skill in the art that this is how z-score is calculated in the art of statistical analysis. See enclosed definition and formula for calculating standard score, also called z-score or normal score, printed from Wikipedia online at < <http://en.wikipedia.org/wiki/Z-score> > on 5/18/06. Thus, Yang et al. implicitly disclosed that the z-score is calculated by subtracting the mean from the intensity data of a replica spot and dividing by the standard deviation for the intensity data.

Yang et al. do not explicitly disclose calculating a first percentage of spots for which the absolute value of the z-score exceeds 1, comparing the percentage with a predefined value, calculating a second percentage for which the absolute value of the z-score exceeds 2, comparing this percentage with a predefined value, calculating a third percentage for which the absolute value of the z-score exceeds 3, and comparing this third percentage with a predefined value.

Churchill teaches fundamentals of experimental design for cDNA microarrays. Churchill analyzes the importance of duplications/replications in designing array experiments, as depicted in Figure 1 on page 491, including treatment replication, biological replication, dye and technical replication, spot and array duplications. Churchill states that “the correlation observed between ratios of fluorescent intensity from duplicate spots on a single microarray slide will typically exceed 95% ... However, if the same target sample is divided and hybridized to two different microarray slides, the correlation across hybridizations is likely to fall to the 60 to 80% range, somewhat lower if the dye labeling is reversed. Correlation between samples obtained from individuals inbred mice may be as low as 30%. If the experiments are carried out in different laboratories, the correlations may be lower still.” See page 490, right column.

Yang et al. state that in analysis of differential gene expression, only genes with a greater than 2 SD from the mean (i.e.  $z > 2$ ) are identified as being significantly differentially expressed. Since Figure 3a represents data from self-self hybridization, it would have been obvious to one of ordinary skill in the art that the elements with a z-score of higher than 2 SD would represent elements with unacceptable variations, and the percentage of the number of such elements on an microarray would indicate the overall quality of the array: the lower the percentage, the higher the quality. Similarly, the percentage of the number of elements with a z-score less than 2 SD,

e.g. more or less than 1, would also indicate the quality of the array: the higher the percentage, the higher the quality of the array. Furthermore, Yang et al. analyzed data variability and reproducibility using triplicates and showed that the spots of outliers in the arrays tested are generally around 5%. See page 0062.5. Yang et al. stressed that replication is essential for ensuring data quality.

One of ordinary skill in the art would have been motivated by Churchill to design microarray experiments using different layers of replications and/or duplications to minimize variations and increase correlations, and motivated by Yang et al. to use self-self hybridizations to evaluate variations and thus quality of the array. Given that the variations in these different replications and/or duplications are different as shown by the different percentage of correlations taught by Churchill, and that the quality of an array would be indicated by the percentage of the number of spots with the absolute values of z-scores of 1, 2 or 3 (i.e.  $>2$ ) as implied by Yang et al. in Fig. 3a, one of ordinary skill in the art would have been motivated by Yang et al. to determine the percentages of the absolute values of z-scores of 1, 2, and 3, respectively, in these different experimental designs with different replications and/or duplications in order to better and more precisely evaluate the quality of an array. It would have been obvious that the higher the percentage of spots with an absolute value of z-score of 1 or less, and or 2 or less, the higher the quality of the array; conversely, the higher the percentage of spots with an absolute value of z-score of 2 or more, and/or 3 or more, the lower the quality of the array. Thus, in a microarray quality control experiment using z-scores, calculating a first percentage of spots for which the absolute value of the z-score exceeds 1, comparing the percentage with a predefined value, calculating a second percentage for which the absolute value of the z-score exceeds 2, comparing

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this percentage with a predefined value, calculating a third percentage for which the absolute value of the z-score exceeds 3, and comparing this third percentage with a predefined value would have been obvious to a person having ordinary skill in the art at the time the invention was made.

### ***Conclusion***

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst Tina Plunkett whose phone number is (571) 272-0549.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete

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service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shubo (Joe) Zhou, Ph.D.

A handwritten signature in black ink, appearing to read 'Shubo Zhou' with a stylized flourish at the end.

Patent Examiner